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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/629,074	07/31/2000	RONALD G CRYSTAL	205965	5286

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EXAMINER
BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 06/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/629,074	Applicant(s) CRYSTAL ET AL.	
	Examin r Anne Baker	Art Unit 1632	

-- The MAILING DATE of this communication app ars on the cover sheet with the corr spondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-12,17,23 and 25* is/are rejected.

7)☒ Claim(s) *4,5,13-16 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The amendment filed March 8, 2002 (Paper No. 9) has been entered. Claims 1, 6, and 22 have been amended.

Claims 1-25 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 8, 2002 (Paper No. 9) has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-12, 17-23, and 25 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 4-10 of the Office Action of Paper No. 5 (mailed 4/24/01) and on pages 4-6 of the Office Action of Paper No. 7 (mailed 11/23/01), because the specification, while being enabling for administering either 1) a vector encoding FGF or VEGF operably linked to a promoter or 2) a vector

encoding FGF or VEGF and a second osteotropic protein each of which is operably linked to a promoter, to a bone or within a tissue immediately surrounding the bone, whereby bone density or formation is enhanced, does not reasonably provide enablement for administration of a first and second nucleic acid to a cell associated with bone, whereby bone density or formation is enhanced, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At page 3, paragraph 3 of the response, Applicants argue that considerable progress has been made on viral targeting and that this technology has been made a part of the instant application by incorporating by reference the text of several patents that concern viral targeting. No specific arguments are offered regarding how these advancements would enable the full scope of the claims, particularly in view of the references cited as evidence that gene therapy is highly unpredictable. However, targeting is not the only issue discussed with regard to lack of an enabling disclosure and, given the state of the art of gene therapy, advances in viral targeting techniques would not be considered sufficient to enable the claimed invention over the full scope because, once delivered, the therapeutic genes must be expressed at a level sufficient to produce the therapeutic effect recited in the claims. The specification and claims contemplate a variety of combinations of angiogenic proteins and osteogenic proteins that can be used in the instant invention. The references cited, including Deonarain (1998), Miller (1995), Verma (1997), and Crystal (1995) highlight the unpredictability in the art of gene therapy and the specific problems associated with obtaining sufficient levels of gene expression to produce a desired effect. Given the unpredictability in the art, the limited guidance in the specification, the limited working examples, undue experimentation would have been required for the skilled artisan to practice the claimed invention over the full scope.

At page 3, paragraph 4 of the response, Applicants argue that hedgehog proteins are osteogenic proteins that can cause bone production *in vivo*. In view of the references cited, the Examiner accepts that

hedgehog proteins are osteogenic. However, the state scope of enablement for the claimed invention is maintained for the reasons discussed above, and reasons of record.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained for reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,942,496 (Bonadio et al., 8/24/99), for reasons of record advanced on pages 16-17 of the Office Action of Paper No. 5 (mailed 4/24/01) and on page 7 of the Office Action of Paper No. 7 (mailed 11/23/01).

The claims are directed to a viral vector comprising at least one first nucleic acid encoding at least one angiogenic protein and at least one second nucleic acid encoding at least one osteogenic protein.

Bonadio et al. (1999) teaches administration of a nucleic acid encoding FGF and a second osteotropic protein to bone progenitor cells. Claim 33 of Bonadio et al. specifically recites the use of an

adenovirus vector having a DNA insert comprising one or more osteotropic genes. The instant specification discloses, at page 3, line 11, that FGF is an angiogenic protein. See Claim 40 of Bonadio et al. which clearly shows that an FGF gene can be used in combination with a PTH gene or a BMP gene as recited in Claim 34 from which Claim 40 depends. Both PTH and BMP are disclosed as osteogenic proteins in the instant specification (page 3, lines 18-38).

At page 4, paragraph 2 of the response, Applicants argue that Bonadio et al. does not disclose or suggest a viral vector that has two transgenes, one encoding an angiogenic protein and one encoding an osteogenic protein. However, as discussed above FGF is considered an angiogenic protein and the claims, particularly Claim 40, contemplates using an FGF-encoding nucleic acid in combination with a PTH-encoding gene or a BMP-encoding gene, both osteogenic proteins, as defined in the instant specification.

Thus, the rejection is maintained, for reasons of record.

Conclusion

Claims 4, 5, 13-16, and 24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER